REMARKS

The presently claimed invention features methods screening individuals for participation in a clinical drug trial by determining whether an individual has the 6/6 genotype, the 6/7 genotype, or the 7/7 genotype at the UDP glucuronosyltransferase subfamily 1 (UGT1) locus. Such determinations are useful in the design and conduct of clinical trials because, as the current specification explains, certain genotypes are associated with increased serum bilirubin, for example, under conditions of restricted diet (see page 17 of the specification).

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 15-18, 21 and 22 as allegedly obvious in view of Bosma et al. (*New England J. Med.* 333:1171, 1995) taken with Sibille et al. (*Eur. J. Clin. Pharmacol.* 39:475, 1990) and Comings (U.S. Patent 5,260,196). Claims 15-18, 21 and 22 have been cancelled. The newly added claims are drawn methods screening individuals for participation in a clinical drug trial by determining whether an individual has the 6/6 genotype, the 6/7 genotype, or the 7/7 genotype at the UDP glucuronosyltransferase subfamily 1 (UGT1) locus.

The Examiner argues that it would have obvious to perform the testing described by Bosma et al. for particular genotypes associated with Gilbert's Syndrome in patients selected for a clinical trial as suggested by Sibille et al.

Sibille et al. does not mention Gilbert's Syndrome, much less suggest that suffering from or at risk of developing Gilbert's Syndrome be excluded from clinical trials. As the Examiner notes, Sibille et al. states that "the aim or laboratory screening in phase I is to exclude subjects with subclinical illness, who might be at increased risk in the study, and who might also adversely influence interpretation of the results". Thus, Sibille et al does suggest that certain laboratory test be relied on to exclude certain patients from clinical trials. Among the various tests suggested by Sibille et al. is a test of serum bilirubin. Sibille et al. suggest that individuals with serum bilirubin levels above 27 μmol/l be excluded from clinical trials (see Table 4).

Bosma et al. tested a number of normal individuals, i.e., individuals that had not been diagnosed as suffering from Gilbert's Syndrome in order to determine if they had the 6/6 genotype, the 6/7 genotype, or the 7/7 genotype at the UDP glucuronosyltransferase subfamily 1

(UGT1) locus. As can be seen in Figure 3, individuals with 6/6 genotype (both normal alleles), the 6/7 genotype (one normal and one mutant allele), or the 7/7 genotype (both mutant alleles) had a serum bilirubin level below 1 mg/dl on average. As Bosma et al. note, 1.0 mg/dl bilirubin corresponds to 17.1 μmol/l bilirubin (see page 1172, left column). Thus, all of the normal individuals, regardless of genotype within the promoter, had a serum bilirubin level well below the 27 μmol/l cut-off cited by Sibille et al. for exclusion form a clinical trial. Bosma et al. also studied 10 individuals diagnosed with Gilbert's Syndrome. These patients had a serum bilirubin level of between 20 and 90 μmol/l. All of these individuals had the 7/7 genotype, the same genotype as many of the normal individuals with far lower serum bilirubin levels Put simply, mutant genotypes investigated by Bosma et al. do not yield a phenotype that Sibille et al. would exclude from clinical trials since some individuals with 7/7 genotype have normal bilirubin levels and others do not. Bosma et al. simply does not demonstrate a correlation between genotype and phenotype that would suggest the usefulness of the genetic test as a criteria for clinical trials according to the standards described by Sibille et al. Thus, Bosma et al. and Sibille et al., no matter how combined, would not lead one skilled in the art to screen candidates for clinical trials in order to determine if they possessed the 6/6/, 6/ or 7/7 genotype. Accordingly, the combination of Bosma et al. and Sibille et al. cannot be seen as rendering the currently claimed invention obvious.

Comings concerns the use buccal smears as a source of DNA for genetic analysis, and adds nothing of significance with regard to the methods of the present claims.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.